

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 223-404-WO	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/EP2004/051283	International filing date (day/month/year) 29.06.2004	Priority date (day/month/year) 13.08.2003	
International Patent Classification (IPC) or national classification and IPC C07D453/02, A61K31/439, A61P25/00			
Applicant NEUROSEARCH A/S et al			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> (<i>sent to the applicant and to the International Bureau</i>) a total of 3 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input checked="" type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 06.06.2005	Date of completion of this report 04.07.2005		
Name and mailing address of the International preliminary examining authority:  European Patent Office - P.O. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized Officer Bosma, P Telephone No. +31 70 340-3665	



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**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - international search (under Rules 12.3 and 23.1(b))
 - publication of the international application (under Rule 12.4)
 - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-12 as originally filed

Claims, Numbers

1-17 received on 08.06.2005 with letter of 06.06.2005

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
- 3. The amendments have resulted in the cancellation of:
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):
- 4. This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - the entire international application,
 - claims Nos. 17 with respect to IA
because:
 - the said international application, or the said claims Nos. 17 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - no international search report has been established for the said claims Nos.
 - the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	<input type="checkbox"/> has not been furnished
	<input type="checkbox"/> does not comply with the standard
the computer readable form	<input type="checkbox"/> has not been furnished
	<input type="checkbox"/> does not comply with the standard

See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-17
	No: Claims	
Inventive step (IS)	Yes: Claims	1-17
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-16
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)
and / or
2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

**INTERNATIONAL PRELIMINARY
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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 17 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). For the assessment of the present claim 17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D3: WO 02/44176 A (JOERGENSEN TINO DYHRING ; NIELSEN ELSEBET OESTERGAARD (DK); AHRING PHI) 6 June 2002 (2002-06-06)

D4: WO 2004/016608 A (JOERGENSEN TINO DYHRING ; NIELSEN ELSEBET OESTERGAARD (DK); AHRING PHI) 26 February 2004 (2004-02-26)

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-17 is new and inventive in the sense of Article 33(2) and 33(3) PCT:

The document D3 is regarded as being the closest prior art to the subject-matter of claims 1-17, and discloses (claims 1-17; examples): 3-substituted quinuclidines having a **bicyclic heterocyclic group**, which is **directly attached** to the quinuclidine ringsystem, which compounds are useful in medicaments for the treatment of diseases or disorders related to the cholinergic system of the central nervous system (neurodegenerative disorders).

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The subject-matter of claims 1-17 therefore differs structurally from this document D3 in being 3-substituted quinuclidines having a **tricyclic moiety attached** to the quinuclidine ringsystem **via the specific linker X**, being e.g. an oxygen or sulfur atom, or a methylene moiety (see dependent claim 4).

It is therefore considered that due to these structural differences the present specific compounds according to claims 1-6, and also the specific use as cholinergic system active agents of such 3-substituted quinuclidines having a tricyclic moiety attached to the quinuclidine ringsystem via the specific linker X, as described in the present claims 7-17, have not been described nor suggested by any of the available prior art documents, which renders these claims new and inventive.

Industrial applicability

The present compounds are useful in medicaments for the treatment of diseases or disorders related to the cholinergic system of the central nervous system (neurodegenerative disorders).

For claim 17 see Box III above.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-2004/16608	26.02.2004	12.08.2003	14.08.2002 02.10.2002

D4 has been cited in the international search report.

D4 contains subject-matter (see example G; claims), which could be of interest for the novelty of the present claims 1-17 (Rule 64.1, 64.3, 70.10 PCT).

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed

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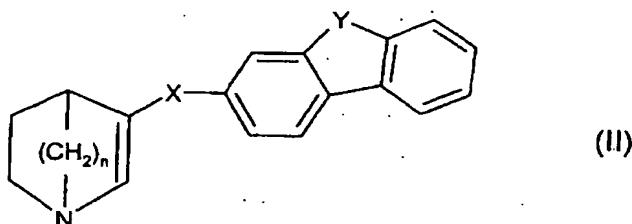
International application No.

PCT/EP2004/051283

in the document D3 is not mentioned in the description, nor is this document identified therein.

CLAIMS

1. A quinuclidine derivative represented by Formula II

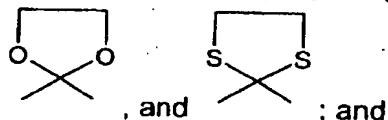


wherein

— represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -S-, -SO-, -SO₂-, -CH₂-, -C(=CH₂)-, -NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



Y represents O, S, SO₂, or NR', wherein R' represents hydrogen or alkyl.

2. The quinuclidine derivative of claim 1, wherein — represents a single (covalent) bond.

3. The quinuclidine derivative of either one of claims 1-2, wherein n is 1, 2 or 3.

4. The quinuclidine derivative of any one of claims 1-3, wherein X represents a linker selected from -O-, -S-, and -CH₂-.

5. The quinuclidine derivative of any one of claims 1-4, wherein Y represents O, S, SO₂, or NR', wherein R' represents hydrogen or alkyl.

6. The quinuclidine derivative of claim 5, which is
(±)-3-(Dibenzofuran-2-yloxy)-1-azabicyclo[2.2.2]octane;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

7. A pharmaceutical composition comprising a therapeutically effective amount of a quinuclidine derivative of any one of claims 1-6, or a pharmaceutically-acceptable addition salt thereof.

8. Use of a quinuclidine derivative of any one of claims 1-6, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors.

9. The use according to claim 8, wherein the disease, disorder or condition relates to the central nervous system.

10. The use according to claim 9, wherein the disease, disorder or condition is anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, psychosis, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, peripheral neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

11. The use according to claim 8, wherein the disease, disorder or condition are associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

12. The use according to claim 8, wherein the disease, disorder or condition is related to the endocrine system, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.
13. The use according to claim 8, wherein the disease, disorder or condition is a neurodegenerative disorders, including transient anoxia and induced neuro-degeneration.
14. The use according to claim 8, wherein the disease, disorder or condition is an inflammatory disorder, including inflammatory skin disorders such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.
15. The use according to claim 8, wherein the disease, disorder or condition is mild, moderate or even severe pain of acute, chronic or recurrent character, pain caused by migraine, postoperative pain, phantom limb pain, neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.
16. The use according to claim 8, wherein the disease, disorder or condition is associated with withdrawal symptoms caused by termination of use of addictive substances, including nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.
17. A method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a quinuclidine derivative of any one of claims 1-6.